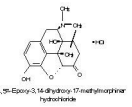
NUMORPHAN - oxymorphone hydrochloride injection
NUMORPHAN - oxymorphone hydrochloride suppository
Endo Pharmaceuticals Inc.

DESCRIPTION

NUMORPHAN (oxymorphone hydrochloride, USP), a semi-synthetic opioid substitute for morphine, is a potent analgesic.



Oxymorphone hydrochloride is a white or slightly off-white, odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water. The molecular weight of oxymorphone hydrochloride is 337.80. The pK_{a1} and pK_{a2} of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.
NUMORPHAN Injection is available in two concentrations, 1 mg/mL, 1 mL ampul and 1.5 mg/mL, 10 mL vial of oxymorphone hydrochloride. In addition, each 1 mg/mL ampul contains 8.0 mg/mL sodium chloride. Each 1.5 mg/mL vial contains 8.0 mg/mL sodium chloride, 1.8 mg/mL methylparaben and 0.2 mg/mL propylparaben. pH for both the ampul and vial is adjusted with hydrochloric acid.
The NUMORPHAN Rectal Suppository is available in a concentration of 5 mg of oxymorphone hydrochloride in a base consisting of polyethylene glycol 1000 and polyethylene glycol 3350.

CLINICAL PHARMACOLOGY

NUMORPHAN is a potent opioid analgesic. Administered parenterally, 1 mg of NUMORPHAN is approximately equivalent in analgesic activity to 10 mg of morphine sulfate.
Many of the effects described below are common to the class of opioid analgesics, including NUMORPHAN.

Central Nervous System (CNS)

Opioid analgesics exert their principal pharmacologic effects on the CNS and the gastrointestinal tract. The principal actions of therapeutic value are analgesia and sedation. The precise mechanism of the analgesic action is unknown. However, specific CNS opiate receptors have been identified and likely play a role in the expression of analgesic effects.
Opioids produce respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation. Opioids depress the cough reflex by direct action on the cough center in the medulla. Opioids cause miosis. Pinpoint pupils are a common sign of opioid overdose but are not pathognomonic. Marked mydriasis may be seen with worsening hypoxia.

Gastrointestinal Tract and Other Smooth Muscle

Opioids decrease gastric, biliary, and pancreatic secretions. These drugs cause a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased while tone is increased to the point of spasm. The end result is constipation. Opioids can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.
Opioids increase smooth muscle tone in the urinary tract and can induce spasms. Urinary urgency and difficulty with urination may result. These effects, in conjunction with the central effect of these drugs on release of vasopressin, may produce oliguria.

Pharmacokinetics

The onset of action of parenterally administered NUMORPHAN is rapid; initial effects are usually perceived within 5 to 10 minutes. Its duration of action is approximately 3 to 6 hours.
Distribution
After an IV dose, the steady state volume of distribution was 3.08 ± 1.14 L/kg in healthy male and female subjects.
Metabolism
Oxymorphone undergoes extensive hepatic metabolism in humans. After a 10 mg oral dose, 49% was excreted over a five-day period in the urine. Of this, 82% was excreted in the first 24 hours after administration. The recovered drug-related products contained the oxymorphone (1.9%), the conjugate of oxymorphone (44.1%), the 6β-carbinol produced by 6-keto reduction of oxymorphone (0.3%), and the conjugates of 6β-carbinol (2.6%) and 6α-carbinol (0.1%).
Elimination
In healthy subjects, the mean terminal half-life of oxymorphone was 1.3 ± 0.7 hours. The mean systemic clearance was 2.0 ± 0.5 L/min.

INDICATIONS AND USAGE

NUMORPHAN Suppository is indicated for the relief of moderate to severe pain.

NUMORPHAN Injection is indicated for the relief of moderate to severe pain. It is also indicated for preoperative medication, for support of anesthesia, for obstetrical analgesia, and for relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction.

CONTRAINDICATIONS

NUMORPHAN should not be administered to patients who are hypersensitive to oxymorphone hydrochloride or to any of the other ingredients in NUMORPHAN, or hypersensitive to morphine analogs.
NUMORPHAN should not be administered to individuals during an acute asthmatic attack or to patients with severe respiratory depression, upper airway obstruction, or any patient who has or is suspected of having a paralytic ileus. NUMORPHAN should not be used in the treatment of pulmonary edema secondary to a chemical respiratory irritant. Opioid analgesics cause pooling of blood in the extremities by decreasing peripheral vascular resistance. This effect results in decreases in venous return, cardiac work, and pulmonary venous pressure, and blood is shifted from the central to peripheral circulation which would not be beneficial in the treatment of pulmonary edema secondary to a chemical respiratory irritant.

WARNINGS

Interactions with Other Central Nervous System Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol) concomitantly with NUMORPHAN may exhibit an additive CNS depression (see **PRECAUTIONS; Drug Interactions**).

Respiratory Depression

NUMORPHAN should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma.

Head Injury and Increased Intracranial Pressure

The possible respiratory depressant effects of potent analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUMORPHAN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Acute Abdominal Conditions

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Drug Dependence

NUMORPHAN, as with other opioid drugs, can produce tolerance, psychological dependence, and physical dependence and has the potential for being abused (see **DRUG ABUSE AND DEPENDENCE**).

Pregnancy

Safe use in pregnancy has not been established (relative to possible adverse effects on fetal development). As with other analgesics, the use of NUMORPHAN in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child (see **PRECAUTIONS**).

PRECAUTIONS

General

Special Risk Patients
NUMORPHAN should be used with caution in elderly and debilitated patients and in patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal or hepatic disease. Caution should also be exercised in patients with hypothyroidism, acute alcoholism, delirium tremens, convulsive disorders, Addison's disease, gallbladder disease or gallstones, prostatic hypertrophy or urethral stricture, recent gastrointestinal or genitourinary tract surgery, inflammatory bowel disease, diarrhea secondary to poisoning until the toxin is eliminated, diarrhea secondary to pseudomembranous colitis, cardiac arrhythmias, increased ocular pressure, and toxic psychosis. Debilitated and elderly patients and those with severe liver disease should receive smaller doses of NUMORPHAN.

Hypotensive Effect
Opioid analgesics may cause severe hypotension in patients whose ability to maintain blood pressure has been compromised by a depleted blood volume or coadministration of drugs such as phenothiazines or general anesthetics. Administer with caution to patients

in circulatory shock, since vasodilatation produced by the drug may further reduce cardiac output and blood pressure. Orthostatic hypotension may occur in ambulatory patients.

Information for Patients

Patients should be cautioned regarding the following:

Drowsiness, dizziness, or lightheadedness related to the use of this medication may impair mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car, operating machinery, etc.

This medication, like other opioid analgesics, will add to the effect of alcohol and other CNS depressants [such as antihistamines, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, tricyclic antidepressants, and monoamine oxidase (MAO) inhibitors]. Alcohol should not be consumed while taking NUMORPHAN.

Withdrawal side effects may be precipitated by suddenly stopping this drug after prolonged use (regular use for several weeks or more). The medication should be gradually reduced before completely discontinuing use.

Elderly patients are more sensitive to opioid analgesics, especially the respiratory depressant effects and opioid induced urinary retention. Lower doses or longer dosing intervals may be required.

Orthostatic hypotension may occur with the use of this medication, especially in ambulatory patients. Patients should get up slowly from a lying or sitting position.

NUMORPHAN (oxymorphone hydrochloride, USP) may be habit forming and has the potential for being abused. Tolerance, psychological and physical dependence can occur.

Safe use in pregnancy has not been established. Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence, and neonatal withdrawal may occur.

Laboratory Tests

Opioids may increase biliary tract pressure with resultant increases in plasma amylase or lipase.

Drug Interactions

The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, and alcohol may produce additive CNS depressant effects. When such combined therapy is contemplated, the dose of one or both agents should be reduced (see **WARNINGS**).

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

It has been reported that the incidence of bradycardia was increased when oxymorphone was combined with propofol for induction of anesthesia.

In addition, CNS toxicity has been reported (confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; no clear-cut cause and effect relationship was established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed in animals to evaluate the carcinogenic potential of NUMORPHAN. Studies to evaluate the mutagenic potential of NUMORPHAN have not been conducted. There have been no studies to evaluate the effect of NUMORPHAN on fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C: NUMORPHAN was reported to produce malformations in offspring of hamsters that received 1,500 times the recommended human dose on Day 8 of gestation. There have been no adequate and well-controlled studies of reproductive toxicity in other laboratory animals or in pregnant women. It is not known whether NUMORPHAN can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. As with other opioid analgesics, the use of NUMORPHAN in pregnancy or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child.

Non-teratogenic Effects

Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence. Neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.

Labor and Delivery

NUMORPHAN should be used with caution during labor. Sinusoidal fetal heart rate patterns may occur with the use of opioid analgesics.

Opioid analgesics in therapeutic doses may prolong labor. Generally, the effect of opioids on the pregnant uterus appears to depend on the time of administration; administration of the drugs during the latent phase of the first stage of labor, or before cervical dilation of 4-5 cm has occurred, may hamper the progress of labor.

Opioid analgesics, including NUMORPHAN, may cause respiratory depression in the newborn. The effect of NUMORPHAN, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers
It is not known whether NUMORPHAN is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when NUMORPHAN is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of NUMORPHAN in pediatric patients below the age of 18 years have not been established.

ADVERSE REACTIONS
As with all potent opioid analgesics, possible side effects when using NUMORPHAN include:
Central Nervous System
Drowsiness, sedation, lightheadedness, unusual tiredness or weakness, headache, dysphoria, euphoria, miosis, diplopia, blurred vision, nervousness, restlessness, confusion, mental clouding, trouble sleeping, paradoxical CNS stimulation, hallucinations, mental depression.
Gastrointestinal System
Nausea, vomiting, dry mouth, constipation, biliary tract spasm, cramps or pain, loss of appetite, paralytic ileus or toxic megacolon in patients with inflammatory bowel disease.
Cardiovascular System
Hypotension, orthostatic hypotension particularly in ambulatory patients, tachycardia, bradycardia, palpitations, flushing.
Respiratory System
Respiratory depression, atelectasis, allergic bronchospastic reaction, allergic laryngeal edema, allergic laryngospasm.
Genitourinary System
Ureteral spasm, urinary hesitancy or retention, antidiuretic effect.
Dermatologic
Itching, sweating, injection site reaction, allergic reaction (such as skin rash, hives, and/or itching, swelling of the face).

DRUG ABUSE AND DEPENDENCE
NUMORPHAN is a Schedule II opioid and is subject to the Federal Controlled Substances Act.
NUMORPHAN, as with other opioid drugs, can produce tolerance, psychological dependence, and physical dependence and has the potential for being abused. The addiction potential of the drug appears to be about the same as for morphine.
Withdrawal symptoms may occur when opioids are abruptly discontinued after prolonged use. Withdrawal symptoms may be characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep, and mydriasis during the first 24 hours. These symptoms often increase in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, twitching, and spasms of muscles; kicking movements; severe backaches; abdominal and leg pains; abdominal and muscle cramps; hot and cold flashes; insomnia; nausea, anorexia, vomiting, intestinal spasm, diarrhea, coryza, and repetitive sneezing; increase in body temperature, blood pressure, respiratory rate and heart rate. Because of excessive loss of fluids through sweating, vomiting and diarrhea, there is usually marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse can occur. Without treatment most observable symptoms disappear in 5-14 days; however, there appears to be a phase of secondary or chronic abstinence which may last for 2-6 months characterized by decreasing insomnia, irritability, and muscular aches. In addition, the patient may have miosis and a slight lowering of blood pressure, pulse rate, and body temperature; respiratory centers exhibit a decreased response to the stimulatory effects of carbon dioxide.
The dose of NUMORPHAN should be gradually reduced before discontinuation in those patients who require treatment for physical dependence.
Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see **PRECAUTIONS; Usage in Pregnancy**).

OVERDOSAGE

Signs and Symptoms
Serious overdosage with NUMORPHAN is characterized by respiratory depression, (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment
Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride (NARCAN®) is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids including oxymorphone. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4 mg-2 mg) preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxymorphone may

exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.
Naloxone hydrochloride should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In addition, it should be considered that the use of an opioid antagonist in patients physically dependent on opioids may precipitate an acute withdrawal syndrome that cannot be readily suppressed while the action of the antagonist persists. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.
Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION
Smaller doses of NUMORPHAN than those recommended below should be used for debilitated and elderly patients and those with severe liver disease.

Usual Adult Dosage of NUMORPHAN Injection
Subcutaneous or intramuscular administration: initially 1 mg to 1.5 mg, repeated every 4 to 6 hours as needed. Intravenous: 0.5 mg initially. In non debilitated patients the dose can be cautiously increased until satisfactory pain relief is obtained. For analgesia during labor 0.5 mg to 1 mg intramuscularly is recommended.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Usual Adult Dosage of NUMORPHAN Rectal Suppositories
One suppository, 5 mg, every 4 to 6 hours. In non debilitated patients the dose can be cautiously increased until satisfactory pain relief is obtained.

HOW SUPPLIED

For Injection
DEA Order Form Required
1 mg/mL 1 mL ampuls
(paraben/sodium dithionite-free) (box of 10) NDC 63481-444-10
1.5 mg/mL 10 mL multiple dose vials
(sodium dithionite-free) (box of 1) NDC 63481-445-01
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]
Protect from light.

For Rectal Suppositories
DEA Order Form Required
5 mg Wrapped in gold foil (box of 6) NDC 63481-761-06
Store under refrigeration 2° - 8°C (36°- 46°F).
Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

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